Clinical relevance of dialysate constituents in hemodialysis treatment: focus on sodium and glucose

Chapter 10

General discussion and summary

General discussion

The aim of this thesis is to evaluate the importance of the dialysate prescription with particular focus on glucose and sodium concentrations, analyse the clinical effects of these serum constituents and emphasize that outcome studies should be based on longitudinal observations in preference to cross-sectional data only.
Despite much literature corroborating this notion, not all aspects of the relationships between dialysate and serum concentration and outcomes are well understood. Due to operational difficulty and a probable increase in effort, individualization of the dialysate prescription rarely occurs as the standard of care in dialysis patients. This thesis in Part A focuses mainly on the importance of differences in dialysate glucose concentration and its consequences. *Part B* focuses on the dialysate sodium concentration (DNa^+) and particularly on its individualization and the relationship between its concentration and pre HD systolic blood pressure (BP) and serum sodium concentration (SNa^+), which could be of importance for BP management. *Part C* examines the need for longitudinal observations and uses the assessment of the relationships of its dynamics to mortality as an example to contrast with the lack of information provided by cross-sectional assessments only. *Part C* in addition contains an analysis of the dynamics of BP and SNa^+

Part A: Glucose

This part consists of three sub-chapters discussing the metabolic and cardiovascular effects of the use of different dialysate glucose concentrations, based on data from 29 hemodialysis (HD) patients participating in a multi-center randomized controlled cross-over trial conducted in both diabetic and non-diabetic subjects in dialysis clinics of the Renal Research Institute, New York, USA in 2008 (*clinicaltrials.gov: NCT00618033*). The last chapter of *Part A* discusses the relationship between SNa^+ and serum glucose in a retrospective analysis of 208 chronic HD patients.
Chapter 2 discusses the metabolic effects in both diabetic and non-diabetic subjects which are associated with the use of a dialysate glucose concentration of 200 mg/dl (11.1 mmol/l) compared to a concentration of 100 mg/dl (5.5 mmol/l). Several aspects are considered and the pre-existing notions, discussed in detail in the **Introduction** which argued for the use of higher dialysate glucose concentrations are addressed. Higher serum glucose and insulin concentration were observed at the higher dialysate glucose concentration and glucose mass transfer was estimated. The intradialytic mass transfer ranged in our data from -159 g to 22 g and from -158 to -4 g at the lower concentration. These mass transfer values are consistent with previously reported data by Ward et al. who reported an intradialytic glucose gain with a dialysate glucose concentration of 200 mg/dl (11.1 mmol/l) of between 18.2 and 20.6 g[1].
In regard to glucose: the avoidance of high dialysate glucose concentrations is likely to reduce the oxidative effects of glucose[2,3]. Arguments of glucose transfer being of

benefit to nutritional status are doubtful in the light of discouraging results with hypercaloric intradialytic parenteral nutrition[4].

Arguments for improved hemodynamic stability with use of high glucose concentrations of 200 mg/dl (11.1 mmol/l) due to augmentation of refilling and thus maintenance of intravascular volume are presented. Earlier work had suggested improved BP stability during treatments using a dialysate glucose concentration of 200 mg/dl (11.1 mmol/l) as compared to the lower concentration of 100 mg/dl (5.5 mmol/l)[5]. This was not evident in our data in neither diabetic or non-diabetic subjects. We also did not find any evidence of increased occurrence of asymptomatic hypoglycaemia (as defined by the guidelines of the American Diabetes Association[6]) when using lower concentrations, which had been another concern regarding the use of lower concentrations. Lower dialysate glucose concentrations appear to be non-inferior in terms of adverse events and beneficial in terms of not causing high serum glucose and insulin concentrations. Benefits of using lower dialysate glucose concentrations were hypothesized in terms of better phosphorus and potassium removal during HD. Since higher serum insulin concentrations induce a significant translocation of potassium and phosphorus from the extra- to the intracellular compartment and this mass may hypothetically not be available for clearance by the dialyzer, potassium and phosphorus levels were of interest in our research[1,7]. However, our data did not confirm that any differences in solute uptake triggered by different levels of insulin caused any difference in their intradialytic concentration. However, we have not performed any direct assessment of mass balance such as fractional direct dialysis quantification[8] (or similar techniques) and thus only are able to negate effects on actual serum concentrations without being able to quantify effects of dialysate glucose concentrations on the mass balance, which may have differed regardless.
These hypothesized effects caused by the differences in potassium concentrations, the effects of potassium on cardiac muscle repolarization and possibly on the occurrence of cardiac arrhythmia was not reflected in the 24-hour Holter recordings. Overall, beneficial outcomes with the use of lower dialysate glucose concentrations in both diabetic and non-diabetic subjects without consequent disadvantageous effects on metabolism or on the cardiovascular system were found.

Chapter 3 presents additional aspects of the analysis of Holter recordings during dialyses using two different dialysate glucose concentrations analysing their relationship to heart rate variability. From this analysis it was evident that diabetic subjects generally had reduced power in all indices regardless of the dialysate used, in keeping with all previous analyses of this kind. Reduced power was particularly noted in the lower frequency band of heart rate variability, which is reflective of sympathetic activation. This was indicative of progression of diabetic neuropathy affecting the

autonomic nervous system and hypothesized to be a contributing factor to the increased incidence of intradialytic morbid events in diabetic subjects[9].

Increased parasympathetic activation was found with higher dialysate glucose concentrations but without any effects on systolic and diastolic BP. This finding is in line with the work by Kanaley et al. who reports comparable findings of increased parasympathetic activation following a glucose load in the general population[10].
The response to high glucose levels could be to induce a neurogenic insulin response from the pancreas and, as a side effect, affect heart rate variability. This is purely speculative, but could be an interesting field of future research. Non-linear HRV indices reflecting entropy in the HRV of the studied subjects did not differ between regimens. Overall **Chapter 3** confirms the lack of effect on hemodynamic stability by the glucose level intervention this however does not entirely negate an, the increased risk of adverse effects in patients prone to intradialytic morbid events by the aforementioned parasympathetic activation caused by glucose loading.

Chapter 2 and **Chapter 3** establish the metabolic and cardiovascular effects of the use of different dialysate glucose concentrations. **Chapter 4** evaluates the effects of the aforementioned glucose mass transfer from and to the patient during the treatment on fatigue. Fatigue was assessed using the Fatigue Severity Scale[11], which quantifies on a scale from 1 to 7 (with 7 reflecting the highest degree of fatigue). This survey showed in addition to increased parasympathetic activation that diabetic subjects are more fatigued than non-diabetic subjects at both studied dialysate glucose concentrations studied. As an additional finding diabetic subjects were more fatigued when receiving HD with a higher dialysate glucose concentration due to reasons which remain speculative. Notably diabetic subjects did also report levels consistently higher than in healthy subjects[11]. However, as causal factors the differences in autonomic activation per se and possible influences of greater insulin concentrations on potassium levels cannot be excluded with sufficient certainty.
Serum glucose concentrations also affect electrolyte concentrations so that at increased glucose concentrations SNa^+ may need to be adjusted. This is necessary because of translocation of intracellular fluid to the extracellular compartment due to the osmotic activity of glucose. This phenomenon is discussed in more detail in **Chapter 5**, where analyzed data from our database was used to estimate the effect of high glucose concentrations on pre dialysis SNa^+ in poorly controlled diabetic HD patients.
Even when DNa^+ is aligned to the SNa^+, aiming to produce neutral intradialytic diffusive sodium balance (**Chapter 6**), the effects of glucose and diabetic management on SNa^+ are of importance, because intradialytic fluid shifts between compartments follow osmotic gradients almost immediately and may lower SNa^+ quickly. In addition the choice of dialysate glucose concentration may determine the increase or decrease of

serum glucose and insulin, as reported in **Chapter 2,** and may separately effect changes in SNa^+ during the treatment. In summary: If the treatment has the potential in those with high serum glucose levels to lower the serum concentration prior to the treatment, a DNa^+ chosen based on the pre HD SNa^+ may be too low and could result in a negative GNa^+ with possible adverse consequences. This remains subject to future research but is of importance in regard to the magnitude of the effects reported. The clinical rule of thumb is that an increase of 100 mg/dl serum glucose lowers the SNa^+ by 1.6 mEq/l as long as the osmotic gradient between the intra- and extra-cellular compartment persists. A comparable correction factor of 1.5 mEq/l per 100 mg/dl holds true for dialysis patients prior to HD treatment (**Chapter 5**). The knowledge of these relationships are possibly of great importance for DNa^+ to SNa^+ alignment, the subject of **Chapter 6**, which is an approach aiming to reduce intradialytic mass transfer,

Part B: Sodium

The largest DNa^+ to SNa^+ alignment project to this date, aimed at providing neutral diffusive sodium balance during dialysis, was conducted in dialysis clinics in Connecticut, USA, previously using a routine DNa^+ of 137 mEq/l. Patients presenting with a SNa^+ below 137 mEq/l, were subject to DNa^+ to SNa^+ alignment. **Chapter 6** outlines the importance of sodium alignment and describes an approach of centrally administering DNa^+ to SNa^+ alignment routinely in the clinic of a dialysis provider network in the US.

The approach makes alignment operationally feasible since it relies on historic data of SNa^+ which is considered to be relatively stable over time allowing the estimation of the actual current SNa^+ based on the average of the preceding 4 months. In essence, alignment should result in a reduction of intradialytic mass transfer and consequently a reduction in interdialytic weight gain (IDWG) and BP.
The approach used for this project includes the influences of seasonal change by utilizing preceding 4 months of a year to predict the coming month with relatively little information gain by the inclusion of additional months' data (**Chapter 6**). Based on data obtained from this quality initiative which we analyzed designed as a retrospective matched cohort study (clinicaltrials.gov #NCT01825590), we found beneficial effects of alignment in terms of pre dialysis weight reduction [-2.2 (95% CI -4.6 to 0.08) kg] and BP reduction [-7.6 (95% CI -13.9 to 1.3) mmHg] in those who were aligned. This suggests that alignment facilitates BP control and may aid to lower post HD target weights, possibly without causing increases in the occurrence of intradialytic hypotension dePaula et al.[12]. The possible advantage of alignment as opposed to general lowering of dialysate sodium concentrations, which has also been suggested to be beneficial[13,14], is a intradialytic mass balance close to zero. When DNa^+ is lowered across the board without alignment, many patients will also receive HD with strongly negative gradients and subsequently will have sodium removed. Despite reports that a lowering of DNa^+

only results in beneficial effects without causing an increased occurrence of adverse events [13], there is nevertheless a lack of evidence that these findings are generalizable to the overall HD population. The data presented in **Chapter 6** is data from the currently largest project analyzing the effects of alignment and currently additional analyses in larger study populations are underway.

The relative stability of pre dialysis SNa^+ is the fundamental base of the algorithm as shown in **Chapter 6**[15]. However, data in **Chapter 8** suggests this not to be necessarily true and also determines factors causing SNa^+ variability are being identified. Furthermore in the same context it is important to note that the absolute SNa^+ level also has direct effects on systolic and diastolic BP **(Chapter 7)**, which adds an additional complication to BP management.

Chapter 7 focuses on the relationship between SNa^+ and BP. A relationship between sodium and BP was shown in the results of in-vitro experiments[16, 17], during HD[18] and for the pre-HD assessments[19]. He et al. reported a significant slope estimate of SNa^+ in a linear mixed model estimating systolic and diastolic BP {0.65 and 0.36 mmHg, respectively [BP per mmol/l of SNa^+ change]} in data from patients in two urban units in the United Kingdom[19]. As the most exciting aspect He et al. report this relationship to be independent of IDWG and fluid volume expansion, which is, according to Guyton's theorem, the operative vector of pre HD systolic BP in dialysis patients. The exact reasons for these dynamics are speculative. Oberleithner et al. showed direct effects of serum sodium on endothelial cells in the presence of aldosterone[17], which triggered the expression of epithelial sodium channel (ENaC) by the endothelial cell which in turn promotes swelling and stiffening[20,21]. Serum sodium appears to strongly affect the deformability and elasticity of endothelial cells[17]. Further, the elasticity of endothelial cells is a prerequisite of normal endothelial function by control of the stress-induced release of nitric oxide[22]. In addition a recent publication suggested a relationship between serum nitric oxide and BP during salt loading and restriction, and an increase of the nitric oxide inhibitor asymmetric dimethyl-arginine (ADMA) with higher salt intake[23].

His findings sparked interest since the pre HD sodium concentration is at equilibrium (without effects from the dialysis treatment) and serves clinical-decision making. This was the first publication in this thesis based on data from the MONDO Initiative[24], which encompasses data from incident HD patients commencing treatment in 41 countries from four continents[25] and allows the analysis of many outcomes.

Based on data from the MONDO database we studied 16,993 incident HD patients commencing treatment in North America, Europe, Asia and South America how the pre-HD SNa^+ relates to pre-HD systolic and diastolic BP. We followed patients longitudinally for an observation period of 24 months using linear mixed effects models with random slope and intercept and the slopes of SNa^+, IDWG, age, gender, potassium, albumin, calcium, diabetes and dialysis vintage included as fixed effects. The relationship between SNa^+ and BP appears to be a phenomenon independent of all

included covariates, including country and continent of origin, BP levels, SNa^+ levels and to a certain extent independent of medical practice patterns. Due to a lack of available data we were not able to confirm our analyses stratified as per antihypertensive therapy in a comparable fashion to the work of He et al. Notably, the slope estimate was substantially smaller as compared to the data by He et al. (ranging from 0.19 to 0.28 and 0.10 to 0.21 mmHg, respectively, for systolic and diastolic BP per mmol/l of SNa^+ change). The reasons for this cannot be found based on the data available but remain speculative. The lack of information on antihypertensive medication may possibly, at least in part, be a contributing factor.
This is a substantial gain in knowledge on this interesting relationship between SNa^+ and BP and we believe this warrants additional research in order to increase our understanding on the determinants of BP and BP dynamics. This is particularly of importance for those where traditional measures of BP management are not sufficiently effective. It furthermore emphasizes the need to reduce sodium loading from all sources, either on during dialysis or from a diet level or both. **Chapter 7** discusses this in great detail.

Part C: The importance of longitudinal observations.

Cross-sectional observations have been used as a reference to predict outcomes for a long time in medical research. Recently there is a trend to focus on longitudinal observation rather than only cross-sectional analyses.
Recent evidence showed the dynamics of relevant clinical parameters such as IDWG, SBP and body temperature, as well as laboratory parameters such as serum albumin and CRP to be predictive of death and hospitalization. Furthermore it was shown that the dynamics before death are also an early indicator of those being at high risk of death. In this context parameter dynamics were repeatedly suggested to serve the development of safety and alert algorithms allowing the identification and immediate attention of those at increased risk of adverse outcomes such as hospitalizations or death[26-29].
These studies however, did not yet focus on SNa^+, despite the effect that this is a highly relevant factor in human pathophysiology. However, cross sectional studies have shown that low SNa^+ is predictive of an elevated risk of death, which is hypothesized to be a reflection of longstanding comorbidities which lower levels over an extended period of time[30-32]. However, these reports only cover a fraction of the actual information due to their cross-sectional nature. For this reason **Chapter 8** analyzed the dynamics [i.e. variability (quantified as the standard deviation of all measurements during the observation period) and systematic changes (quantified as the slope estimate from a fitted linear model through all available measurements during the observation period)] of SNa^+ over a one year observation period following HD initiation in an international cohort of HD patients. The chapter further aimed to identify the main determinants of these dynamics and the relationship to outcomes. Statistically

significant predictors of SNa^+ variability with a positive relationship were: SNa+, male gender, serum albumin, nPCR, serum potassium, body mass index, DNa+ and North America as a region. In contrast only diabetes, normalized protein catabolic rate and DNa^+ were associated positively with SNa^+ slope. IDWG in turn has an inverse effect on the SNa^+ slope. Based on these data we were further able to find that variability (defined as the standard deviation of SNa^+ measurements over the period of 12 months) and the trend over time (change in SNa^+ over the period of 12 months) associated significantly to death in a study population of 16420 incident HD patients from North America and Europe. To illustrate these relationships we used a novel approach proposed and developed by Yuedong Wang, which allowed plotting of the risk of death in a bivariate fashion as a function of SNa^+ concentration and SNa^+ variability, respectively and slope[33-35]. Increased variability and decreasing SNa^+ was associated with an increased risk of mortality (the latter particularly at lower levels of SNa^+), whereas increasing SNa^+ from low levels of SNa^+ are associated with improved survival. Despite a significant relationship between systematic trends and variability, variability may be an independent predictor of death and may be speculated to be reflective of failing regulatory systems due to comorbidities. More research is required on the determining factors of SNa^+ variability and trends in order to find out how to alter the dynamics of SNa^+ and subsequently improve outcomes.

Chapter 9 focuses on systolic and diastolic BP, its dynamics and its determinants. BP itself is possibly the best described and studied predictor of death in the general population and HD patients. The strength of the relationship has long been known to be of utmost importance [36].

Recently published reports showed relationships to longitudinal observations and in particular the variability of BP to be associated with death in patients suffering from chronic kidney disease and those treated with HD[37-39]. In **Chapter 9** we discuss the dynamics of pre HD BP and their relationship to death. High BP has adverse sequelae such as increased left ventricular mass consequentially leading to an increased risk of death. Conversely, a low BP may not only be a reflection of successful BP management but also the result of continued deteriorating cardiac function and therefore a sign of an adverse pathophysiologic dynamic. A U- or J-shaped curve of the relationship between SBP, DBP and risk of death has been reported for the general population[40] but and for HD patients[36]. HD patients visit dialysis centers thrice-weekly in most cases so that a greater number of measurements are available. This puts the dialysis provider in a unique position to identify those at risk of death with statistical tools. In **Chapter 9** we identified patients at a higher risk of death with increasing and decreasing trends of systolic and diastolic BP regardless of the baseline BP level. This renders longitudinal observation and the consideration of parameter dynamics of great importance for clinical decision making. However, further research is required to evaluate determining factors and, more importantly to identify those which are modifiable to improve survival.

Conclusion

In summary this thesis outlines the importance of the dialysis prescription and shows that the concentrations of both glucose and sodium in the dialysate are important and affecting both soft outcomes and hard outcomes such as death.. This thesis aimed to outline the possible benefits of individualization of sodium concentration in the dialysate and the avoidance of glucose and sodium loading of HD patients. To outline the importance of the metabolism of glucose and sodium the interrelationship between serum glucose and SNa^+, and between SNa^+ and BP was discussed. Additional research is required as to other constituents of the dialysate such as bicarbonate, potassium, phosphorus, and others affect outcomes and how the balance of these solutes could be controlled in the dialysis clinic.
Further this thesis showed that longitudinal observations, at least in HD patients, where regular and high-frequently collected data are available, to be of great information gain when aiming to identify patients at risk of death. It could aid the development of safety and alert algorithms, and predictive models and their implementation. Models may enable the prediction of risk on an individual level and may aid the improvement of outcomes in the HD population, a population at a very high risk of hospitalizations and death. Understanding the dynamics reflected in longitudinal analyses will facilitate the understanding of all relevant relationships between parameters of interest and their association to death. For this purpose the extent as to which each parameter contributes to the information gain using these algorithms needs to be evaluated.

The findings reported in Part A of this thesis need to be confirmed in large international databases such as the MONDO database, in order to confirm the generalizability of these results to an international level. DNa^+ to SNa^+ alignment needs to be studied in adequately powered and randomized research settings.
Meeting the objectives of individualizing the dialysis treatment for every patient and to be able to identify patients at risk of adverse outcomes will only be possible by a close collaboration between governments, dialysis providers, researchers, physicians of many specialties, caregivers and - of course - the patients themselves.

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